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Two versus one high-frequency rTMS session per day for treatment-resistant depression: A randomized sham-controlled trial.

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Abbreviations list: High-frequency repetitive transcranial magnetic stimulation (HF-rTMS); Repetitive transcranial magnetic stimulation (rTMS);treatment-resistant major depression (TRD); Hamilton Depression Rating Scale (HDRS); Clinician Global Impressions-Severity of Illness (CGI-S); Major Depressive Disorder (MDD); randomized controlled trial (RCT); Mini-International Neuropsychiatric Interview (MINI); Structured Clinical Interview for DSM-IV Axis I Disorders (SCID); motor threshold (MT); prefrontal cortex (PFC); first dorsal interosseous (FDI); standard deviation (SD); analysis of variance (ANOVA)

Abstract

Objectives: High frequency repetitive transcranial magnetic stimulation (HF-rTMS) has proven antidepressant effects, but the optimal frequency of sessions remains unclear.

Methods: We conducted a 3-week, sham- controlled trial to assess the antidepressant efficacy of one session/day (A1 Group) compared to two active HF-rTMS sessions/ day (A2 group) and equivalent sham sessions (once/day--S1 Group, twice/ day--S2 Group) in patients with treatment-resistant major depression (TRD), with a subsequent 2-week follow-up period. 177 patients were screened, of whom 105 met eligibility criteria and 98 consented and were randomized. HF-rTMS(20 Hz) was targeted to the left prefrontal cortex in sessions of approximately 40 trains (2 sec each) at 100 % resting motor threshold, with an inter-train interval of 1 min. Treatment response was defined as a ≥50% decrease in Hamilton Depression Rating Scale (HDRS) score and/ or Clinician Global Impressions-Severity of Illness (CGI-S) score ≤3. Remission was defined as HDRS score <8 and/ or CGI-S score ≤2.

Results: Practically none of the subjects in either sham groups achieved remission. Increased odds of remission were present for CGI-S by stimulating twice rather than once per day (OR=1.5, p=0.018) while there was a marginal result for HDRS (OR=3.9, p=0.066). Patients who had lower baseline HDRS (OR=0.75, p=0.014) and CGI-S scores (OR=0.18, p=0.001) were more likely to achieve remission.

Conclusions: Twice per day active HF- rTMS might be more effective than once per day active HF-rTMS or sham stimulation.

Key words: Depression, randomized controlled trial, Transcranial Magnetic Stimulation (TMS).

Introduction

A large number of patients with Major Depressive Disorder (MDD) do not respond to two or more antidepressant medication treatments[1-3]. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method to stimulate the brain[4-6]. Several studies, involving patients with MDD, were conducted with the use of high frequency rTMS (HF-rTMS) [7-9].

HF-rTMS has antidepressant effects in sham-controlled trials[10, 11] and naturalistic studies[12-15], with efficacy supported in several recent systematic reviews and meta-analyses [16-21]. However, there are concerns regarding the quality of some studies [5] and the definition of optimum treatment indications and regimen[22, 23].

One important unresolved issue is the number of times per day that HF-rTMS should be delivered [24]. Loo et al.[25], in a 2-week randomized controlled trial (RCT), found that twice a day HF-rTMS is safe and better than placebo, but did not compare twice a day rTMS with once a day. We are not aware of any study directly comparing twice a day vs. once a day rTMS for treatment of treatment-resistant major depression (TRD). We present here results of a RCT to assess the antidepressant efficacy of two HF-rTMS sessions /day vs. one session/ day vs. sham stimulation once or twice/ day in patients with TRD.

Materials and Methods

Sample Recruitment

The study was approved by the Eginition University Hospital Research Ethics committee and was consistent with the Declaration of Helsinki. The trial protocol with reference n^{o} 0527821514 can

be accessed at http://www.eginitio.gr/Erevna/. The study is registered (http://controlled-trials.com/ ISRCTN71929667). Patients were recruited from the outpatient service of Eginition Hospital, Athens, Greece between July 2006 and December 2011. Eligible subjects had to be 18-59 years old, right-handed, meet DSM-IV-TR criteria[26] for current non-psychotic MDD, be naïve to TMS, and without history of seizures, head injury with loss of consciousness, brain surgery, presence of metallic implants, dementia or other Axis I diagnosis, substance dependence or abuse within the previous 6 months, or pregnancy; Diagnoses were confirmed using the Mini-International Neuropsychiatric Interview (MINI)[27] and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)[28].

Patients had to be at least stage 2 treatment resistant (failure of at least two adequate trials of two different major classes of antidepressant) according to criteria by Thase and Rush[29]. Patients referred for treatment were screened for eligibility. Of the 177 patients screened, 105 were found eligible. All subjects were provided with full written information about the nature and purpose of the study and 98 gave written informed consent to participate (Table 1).

If clinically appropriate, subjects were encouraged to discontinue medication prior to study entry. If this was not possible, subjects were kept on a minimum antidepressant regimen, in order not to risk a recurrence of severe depressive symptoms (venlafaxine 75-112.5 mg/day, mirtazapine 30-45 mg/day, citalopram 20-30 mg/day); if taking benzodiazepines, a dose no greater than the equivalent of 1 mg clonazepam/ day was permitted. The medication regimen was kept stable for at least 4 weeks before study entry and throughout the study period.

Design

The study was a parallel-group, randomized, sham-controlled trial with 4 treatment groups: the once daily active stimulation group (A1), the twice daily active stimulation group (A2), the once

daily sham stimulation group (S1) and the twice daily sham stimulation group (S2) (Table 1). To ensure allocation concealment, following baseline assessment by trained physician-raters, patients were randomly assigned to receive a course of active or sham rTMS once or twice/ day by an independent researcher using a password-protected computer database containing the randomization list. "Treaters" were residents in psychiatry who were blind to the study protocol and naïve to rTMS; they were told this was a study comparing two methods of active rTMS. "Treaters" were not allowed to deliver rTMS outside the study and were advised not to discuss the study protocol with patients and raters.

Patients had 15 (once a day) or 30 (twice a day) treatment sessions on consecutive weekdays (starting Monday) for 3 weeks. All the patients would come in the morning around 8.00 am for the first treatment session (both once and twice a day) and in the afternoon around 5.00 pm if they were scheduled for a second treatment session (only twice a day). Patients and raters were blind to allocated treatment; only physicians responsible for the study protocol (CT, CP, PS) knew the treatment being delivered. To check blinding, patients were asked to guess which treatment had been received ("active TMS," "sham TMS," "can't guess") at the beginning of visit 2 and after visit 15 and raters after visit 15. The period of clinical assessment was extended two more weeks beyond the completion of rTMS sessions because we have an indication that rTMS sometimes produce a late effect for some of the patients.

TMS Procedure

HF-rTMS sessions took place in the TMS Unit, Eginition Hospital, Athens, Greece. At screening, experienced TMS researchers identified and marked on a swim cap (separate for each subject) the vertex, the scalp location for optimal stimulation of the motor cortex (MC) controlling the right

first dorsal interosseous (FDI) muscle, and the point 5 cm anterior to the motor cortex location along a left superior oblique plane (treatment stimulation site-left prefrontal cortex). Subsequently, subjects had structural MRI while wearing the swin cap with attached fiducials (vitamin E capsules) placed over the MC and the left prefrontal cortex (PFC) [30]. If the fiducial intended to be over PFC was actually over the premotor cortex, it was moved 1 cm anterior (this occurred in 34.7% of patients). At the beginning of each treatment session, motor threshold (MT) was determined by delivering single TMS pulses to the motor cortex for the right FDI muscle, with continuous EMG monitoring. MT was defined as the percent output of the stimulator that induced at least a 50-μV motor evoked potential in 5 of 10 single stimulations. After baseline, MT was determined once more at the beginning of the 8th rTMS session.

"Treaters" used a Magstim ultra rapid stimulator (Magstim Company Limited, Whitland, UK), with a figure-eight magnetic coil applied over PFC. Each session of HF rTMS treatment consisted of approximately 40 trains of 20 Hz at 100 % MT, with train duration 2 s and inter-train interval of 1 min, yielding 1600 pulses/session. These stimulation parameters are in accordance with international TMS safety guidelines [31, 32]. Total pulses were 24,000 for the once per day rTMS group and 48,000 pulses for the twice per day rTMS group. For active TMS, the coil was placed flat against the scalp with the handle and short axis of the coil oriented in a parasagittal plane and the intersection of the figure-eight windings centered over PFC. Sham TMS was delivered in the same anatomical location with identical stimulation parameters but with the lateral edge of the coil rotated 90° away from the scalp. The sham subjects went through the same procedures as the active TMS subjects up to the point of the coil rotation.

Outcome Measures

Outcome measures were the 17-item Hamilton Depression Rating Scale score (HDRS- Hamilton, 1960) [33] and the Clinician Global Impressions-Severity of Illness score (CGI-S)[34]. Patients were evaluated at baseline (before randomization) and at the end of the 1st, 2nd, 3rd and 5th week. Additional baseline data obtained by patient interview and case note review included age, sex, past history of depression and ECT, number of medication treatment steps for the current depressive episode (according to the criteria of Thase and Rush[29]), and current antidepressant and/or benzodiazepine medication.

For HDRS, response was defined as a decrease of ≥50% from baseline and remission as HDRS score< 8. For the CGI-S, response was defined as an endpoint rating of 3 or less (corresponding to "mildly ill" or better), whereas remission as an endpoint rating of 2 "borderline mentally ill" (2) or 1 "normal/not at all ill"[34].The inter- rater reliability (intra-class correlation coefficient) for the outcome measures were 0.95 for HDRS and 0.97 for the CGI-S.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD), while qualitative variables are presented as absolute and relative frequencies. Bonferroni post hoc correction for multiple comparisons was used to assess differences in baseline characteristics between groups.

Mixed effects regression was used in order to study the differences in the outcome variables over the 3-week treatment period and the follow-up period and evaluate differences among the four study groups. For each outcome measure, a mixed effects model was employed in order to evaluate the treatment effect during the five weeks course, allowing for different intercept and slope for each individual (the random intercept and slope model constituted an improvement over the

simpler random intercept model, as indicated by the corresponding likelihood ratio tests for nested models: HDRS χ^2 (2)=32.5, p<0.001; CGI χ^2(2)=29.3, p<0.0001).

The reference category for the group was set as the A1 group and the follow up (week 5) in order to facilitate the interpretation of the coefficients in Table 4. The analysis was repeated considering the 5-point time variable as numerical. This approach allows us to consider a quadratic effect for time. One-way analysis of variance (ANOVA) was used to evaluate group differences at the follow-up.

Multiple logistic regression analyses using a stepwise method including various independent variables (i.e., gender, age, stage of treatment resistance according to the Thase and Rush criteria, current antidepressant and benzodiazepine use, HDRS baseline score) were performed to identify predictors of treatment outcome (response or remission), based on HDRS and CGI-S scores. All reported p values are two-tailed and statistical significance was set at 0.05. Analyses were conducted using STATA 13.

Power Analysis

Power analysis methodology for this study represents a design with four levels of the between-subject factor (four treatment groups) and five levels of the within-subjects factor (time in weeks). Sample size was determined using previously published effect size estimates (Avery et al.[35]- differences in rates of response between the sham and TMS groups with a 0.69 effect size) and indicated 90% power for a two-tailed test of significance at p<0.05.

Results

Sample characteristics per study group

177 patients were screened, of whom 105 met eligibility criteria and 98 consented and were randomized (Table 1). The four study groups were similar in terms of age, sex, medication, Rush and Thase stage, and HDRS and CGI- scores at baseline (Table 2). Of the 98 randomized patients, 27 patients received once daily sessions of active HF-rTMS (A1 group), 27 patients received twice daily sessions of active HF-rTMS (A2 group), 20 patients received sham stimulation once per day (S1 group) and 24 twice per day sham stimulation (S2 group). Eighty-nine subjects completed the 5-week trial and nine (9%) discontinued (2 from A1 group; 2 from A2 group; 2 from S1 group; 3 from S2 group) (Table 1): one for protocol violation (a treater discussed study protocol with a patient), two due to exacerbation of pre-existing headache, 5 were unable to attend treatment sessions due to financial and work-related reasons, and one hospitalized with influenza. The basic analysis was conducted on the intent-to-treat sample, i.e., the 96 individuals who had measurements at week 1 (Table 1). The sample was reduced to 89 for models that refer to the differences between baseline and follow-up (for details see the Results section).

Treatment Efficacy

Time course analysis of change of Mean scores for HDRS and CGI-S

There were no significant differences among treatment groups on any baseline measure (Table 2). Table 3 and Figure 1 present the changes in outcome measures over time, for each group separately. The mean scores were significantly different between the A1 group and the other three groups (Week 5- "follow up") for both outcome measures. In particular, the A2 group had significantly lower mean scores than the A1 group, while both sham groups had significantly higher scores. No significant interactions emerged for the A2 group and time, while for the sham groups the interactions were significant, with the exception of the fourth week for CGI-S. In

relation to the score differences between the primary endpoint (3 weeks) and the end of the study (5 weeks), no statistically significant differences were present in the HDRS in the S1 ($p=0.75$) and S2 ($p=0.118$) whilst the differences were significant in the A1 ($p=0.001$) and A2 ($p<0.001$) groups. In the case of CGI, the only significant difference was present in the A2 group ($p=0.046$, whilst $p>0.1$ in all other groups).

--- Table 4 ---

The analysis considering time as a numerical variable yielded similar results. Significant effects emerged for the linear (HDRS: $b_t=1.2$, $p<0.001$ / CGI-R: $b_t=0.3$, $p<0.001$) and the quadratic time (HDRS: $b_{t2}=0.5$, $p<0.001$ / CGI-R: $b_{t2}=0.06$, $p<0.001$). The A1 group had significantly higher mean than the group A2 (HDRS: $b_{A2}=-3.6$, $p=0.026$ / CGI-R: $b_{A2}=-0.7$, $p=0.011$) and lower means than the sham groups (HDRS: $b_{S1}=15.3$, $p=0.026$ – $b_{S2}=17.2$, $p<0.001$ / CGI-R: $b_{S1}=2.3$, $p<0.001$ – $b_{S2}=2.6$, $p<0.001$). No significant interactions with time emerged for the A2 group, but the interactions were again significant for the sham groups ($p<0.001$ in all cases).

Response and Remission

Only one individual (2.5%) in the sham groups had a treatment response based on HDRS score, as opposed to 29 (59.2%) for the active groups ($\chi^2=31.666$, df=1, $p<0.001$). Similarly, only 5 individuals (12.5%) has a response based on CGI-S scores in the sham groups, as opposed to 49 (100%) in the active groups ($\chi^2=70.664$, df=1, $p<0.001$). The logistic regression found that likelihood of a treatment response (in terms of HDRS) in the active rTMS groups was significantly associated only with frequency of rTMS sessions (OR=5.2, $p=0.027$), baseline HDRS score (OR= 0.7, $p=0.010$), and current medication status (OR=5.2, $p=0.033$) (with each OR controlled for the

other two). Logistic regression could not be done for CGI-S scores, as all individuals had CGI-S score ≤ 3.

No one in the sham groups was in remission (based on HDRS) at follow-up, as opposed to 12 (24.5%) of the individuals who received active treatment ($\chi^2=11.323$, df=1, p=0.001). Similar results occurred for remission based on CGI-S (2.5% versus 51% for the sham and active groups, respectively, $\chi^2=25.072$, df=1, $p<0.001$). The logistic regression found that likelihood of remission in the active groups was significantly associated with baseline scores (HDRS OR=0.75, p=0.014; CGI-S OR=0.18, p=0.001) and with number of rTMS sessions per day (CGI-S OR=1.5, p=0.018; HDRS OR=3.9, p=0.066).

Integrity of the Blind

The four treatment groups did not differ significantly in their guesses about which treatment they received after the first (p=0.8) and last rTMS session (p=0.6). Likewise, raters did not guess better than chance which subjects received active treatment (p=0.7). However, the response to rTMS treatment did appear to influence subjects' thoughts about what they received. After the 15th day of rTMS, 100% of the 12 patients (3 from the A1 group and 9 from the A2 group) who achieved remission thought they were receiving active TMS vs. 46.8% of non-remitters (36/77) (p=0.001). Similarly, after the 15th day of rTMS, 82.7% of the patients (24/29) with a treatment response thought they were receiving active TMS vs. 40% (24/60) of non-responders ($p<0.001$).

Adverse Effects

rTMS sessions were generally well tolerated. No seizures occurred. Seven patients from the A1 group, six from the A2 group, five from the S1 group, and six from the S2 group complained of

discomfort at the site of stimulation. Nine subjects (3 from A1 group, 2 from A2 group, 1 from S1 group and 3 from S2 group) experienced exacerbation of pre-existing headache; one subject from A1 group and one from S2 group discontinued the trial because of this. One patient was hospitalized with influenza (not considered study related). There were no significant group differences in proportion of subjects with various adverse effects.

Discussion

Findings

To our knowledge, this is the first randomized sham-controlled trial to compare the effectiveness of twice daily vs. once daily HF- rTMS sessions for treatment of TRD. It is proposed that twice daily sessions might be more effective in terms of both response and remission rates. There was a slight discrepancy, however, between the CGI-S results and HDRS results (increased odds of remission were present for CGI-S by stimulating twice rather than once per day while there was a marginal result for HDRS); yet, other studies have also come across similarly discrepant results when different outcome measures were used[25]. It is of note, that Bandelow et al.[34] suggest that a CGI-S score of 2 or less indicates remission while a CGI-S score of 1 indicates complete or symptom free remission (this might explain the discrepancy observed between the CGI-S remission scores and HDRS-remission scores).

Relation to previous studies

Number of stimulations per session and per day, duration of treatment per weeks

In our study, a 3-week treatment period was used, each session consisted of 1600 pulses (24000 pulses for the A1 group and 48000 for the A2 group for the whole course). Avery et al. [35] in a 3-

week controlled study comparing active and sham stimulation (1600 pulses/day and 24000 pulses for the whole course similar to the A1 group in this study) found response rate to be 31% (compared to 37% for the A1 group in this study) and remission rate 20% (compared to 11% for the A1 group in this study) based on HDRS scores. Nevertheless, results may be different from other RCT studies[10]; various factors could have contributed to this: age of patients, chronicity of the condition, medication, localization of the stimulation point, the frequency of tms stimulation might have also been a factor. We have rarely noticed so good results with frequency of 10 Hz compared to 20 Hz [36].

In the study by O'Reardon et al., [10] stimulation period was extended to 4-6 weeks, Indeed larger stimulation periods might investigate better the efficacy of rTMS; however, withdrawal rate could be high [37]. We have chosen a 3-week stimulation period to retain in the study the larger number of patients possible; this was actually the minimum treatment period suggested in the study by George et al. [11]

Having more rTMS sessions during each day[38-41] and increased number of pulses per day [42-45], as in our study, might retain more patients[37] and have faster antidepressant effects. Within this context, Holtzheimer et al. [42] employed 15,000 rTMS pulses for over 2 days, while Hadley et al. [43] employed 6800 pulses per session and 5 sessions per week (34,000 pulses per week) for 2 weeks (10 sessions). MacDonald et al. [44] found that patients who remitted during fast left-sided treatment received a mean of 26 active treatments (90,000 pulses). Finally, George et al. [45] delivered 54,000 pulses of left prefrontal rTMS over three days to suicidal inpatients and found high doses of rTMS to be feasible and safe over a short treatment period. We think that the number of pulses per day is a very significant factor for remission; however many patients, especially the ones experiencing

adverse effects may need more sessions per day, because they cannot tolerate increased number of pulses per session.

Adverse effects

The treatment was relatively well tolerated, with no significant difference in adverse effects between rTMS and sham groups or between once daily and twice daily sessions and high retention rate (90.8%) HF-rTMS has previously been found safe even in patients with serious physical conditions [46].

Factors influencing response and remission

Both twice daily rTMS sessions and concurrent antidepressant medication were associated with better treatment response. Recently, it has been proposed [11, 47] that greater rates of response and remission would be seen if TMS were delivered in combination with pharmacotherapy. Several studies[48-50] and meta-analyses[51, 52] suggest that HF-rTMS may accelerate response to antidepressants and provide clinical improvement comparable to triidothyronine and pindolol augmentation. In the present study, we found that patients on antidepressants exhibited greater response but not greater remission rates, possibly due to short follow-up period.

In previous studies, younger age[12, 53, 54], less treatment resistance[53, 55, 56], lower baseline symptom severity[12, 54], and lack of comorbid anxiety disorders [56] were associated with better response. In our study, no effect was found regarding age, possibly because all our patients were relatively young; we did find the expected association with lower baseline symptom severity, but not with TRD stage[29]. We did not examine the presence of comorbid anxiety disorders. Carpenter et al.[12] found that TRD level was a modest predictor of benefit from TMS treatment, while, Shutter [8] also reported that treatment resistance does not play a major role in TMS antidepressant effect. Finally,

Demitrack and Thase[57] found rTMS efficacy to be similar to that of antidepressant therapy or atypical antipsychotic augmentation in TRD.

Blinding and placebo effects

"Treaters" were not blind to treatment allocation, potentially jeopardizing the blinding of subjects. Furthermore, we did not have a sham coil that could deliver somatosensory sensations matched to active stimulation[11]. Sham TMS consisted of active pulses delivered to the same anatomical location with identical stimulation parameters but with the lateral edge of the coil rotated 90° away from the scalp. This sham rTMS approach produced acceptable levels of blinding in previous studies [58]. Furthermore, debriefing data from both the patients and raters indicated that the blind was successfully maintained. George et al.[11] reported that 48% of clinical raters guessed correctly (35% correct for active rTMS and 59% for sham) while 84% of their guesses were not confident. Lisanby et al.[59] found that tilting the coil at a 90° angle, like in the present study, produced minor therapeutic effects (only 29% of the peak integrated voltage of the actual TMS stimulation). In our study, sham rTMS appeared to have no therapeutic effect, as only one subject in the sham groups had any treatment response. In other studies a larger response and remission rate were observed for the sham stimulation group [11, 35]. George et al. [11] reported that those patients who remitted either in the sham or the active group seemed to be less resistant to treatment. It is possible that our patients were more resistant to treatment than the ones in other studies[11, 35]. For example, in the study by Avery et al.[35] very similar to ours (for what concerns stimulation parameters and sham condition), the TMS group and sham group differed by 25% ((11/35) 31% -6% (2/33)) in response rate and by 17% ((7/35) 20% - 3% (1/33)) in remission rate. In our study, A1 group and S1 group differed in response rate by 32% ((10/27) 37% - 5% (1/20)) while remission in the two groups differed by 11% ((3/27) 11% - 0% (0/20)).

It is worth noting that there was a greater remission rate in the study by Avery et al. [35] both for the active and sham group. In our study only 3/27 subjects (11%) from A1 group remitted compared to 7/35 (20%) in the active group and 1/33 (3%) in the sham group in the study by Avery et al.[35].

Localization of PFC

Precise PFC location could increase TMS efficacy[11, 60]. We used structural MRI to locate PFC; in 34.7% of patients PFC was found in a more anterior position than the one dictated by the 5 cm rule.

Study Limitations

A number of study limitations should be taken into account. First, raters and "treaters", though blind to the study protocol, were from the same academic center. Second, we were not able to evaluate cognitive function; however, several studies have indicated that rTMS is relatively safe in this domain[25, 61]. Third, the follow-up period was short because we did not want TRD patients to remain untreated for longer periods. This study cannot comment on the duration of effects beyond two weeks.

Conclusions

Twice per day active HF- rTMS might be more effective than once per day active HF-rTMS in patients with TRD. Larger multi-centered studies should verify the above-mentioned results.

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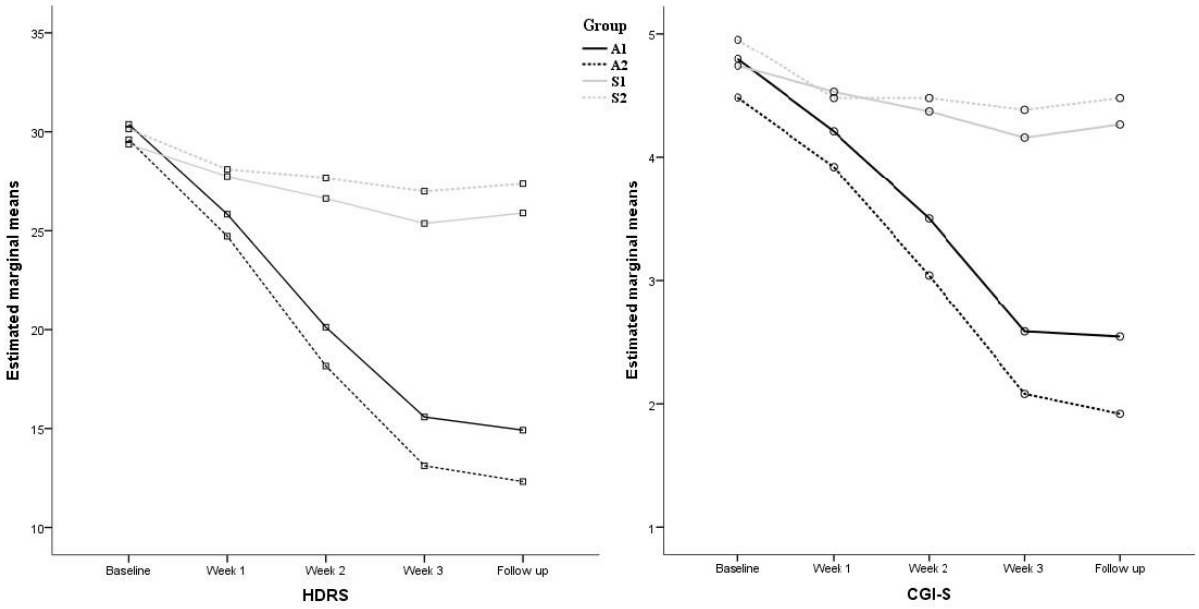
Estimated marginal means
35
30
25
20
15
10
Baseline
Week 1
Week 2
Week 3
Follow up
HDRS
Group
A1
A2
S1
S2
Estimated marginal means
5
4
3
2
1
Baseline
Week 1
Week 2
Week 3
Follow up
CGI-S

Figure 1

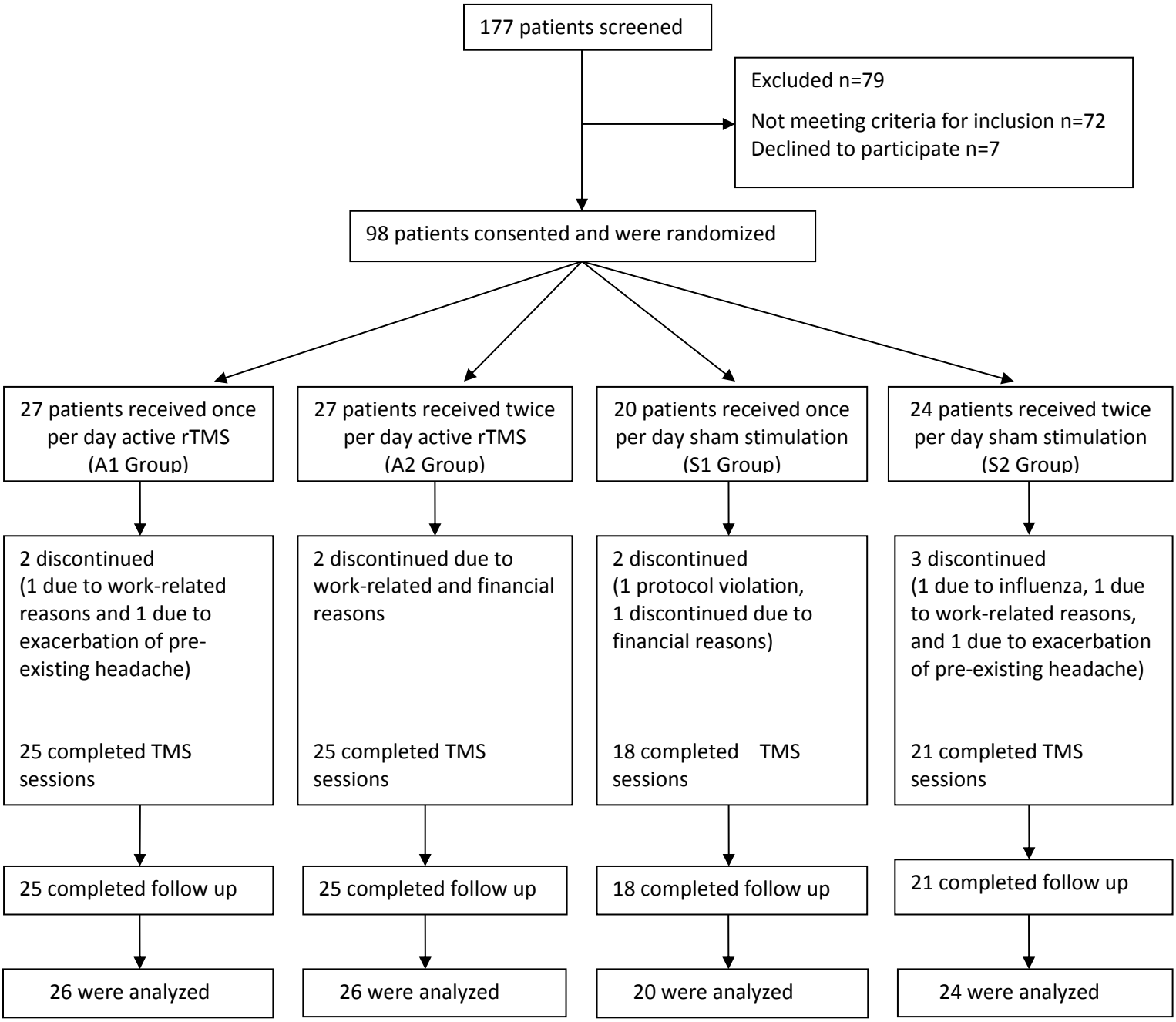

Table 1: Flow Chart

Table 2: Baseline characteristics (per group) of adults with treatment-resistant major depression receiving HF rTMS treatment (N=96).

	Treatment Group				Difference between groups
	A1	**A2**	**S1**	**S2**	
Age (years): Mean (sd)	39.1 (10.1)	38.9 (13.9)	38.0 (9.9)	39.4 (8.9)	F(3,92)=0.070, p=0.976*
Gender: N (%) of males	11 (44.0)	15 (57.7)	10 (47.6)	14 (58.3)	χ^2=1.526, df=3, p=0.676
Medication: N (%) of receiving	14 (56.0)	16 (61.5)	9 (42.9)	15 (62.5)	χ^2=2.008, df=3, p=0.530
Rush and Thase stage: N (%) of ≥4	7 (28%)	6 (23%)	4 (18%)	7 (29%)	χ^2=0.660, df=3, p=0.883
HDRS at baseline: Mean (sd)	30.6 (3.2)	29.7 (4.6)	29.4 (3.2)	30.3 (3.6)	F(3,92)=0.529, p=0.663*
CGI-S at baseline: Mean (sd)	4.8 (0.6)	4.5 (0.6)	4.8 (0.7)	5.0 (0.7)	F(3,92)=2.677, p=0.052*

** Bonferroni post hoc correction indicated no differences between groups.*
Abbreviations: A1: Active rTMS-- 1 session/day, A2: Active rTMS-- 2 sessions/day, S1: Sham rTMS--1 session/day, S2: Sham rTMS--2 sessions/day.

Table 3: Mean (standard deviation) for the two outcome measures at each time point, per group.

		Group			
		A1	**A2**	**S1**	**S2**
HDRS	**baseline**	30.6 (3.2)	29.7 (4.6)	29.4 (3.2)	30.3 (3.6)
	Week 1	26.2 (3.8)	24.9 (4.2)	28.2 (4.7)	28.7 (4.1)
	Week 2	20.1 (3.6)	18.2 (4.6)	26.6 (4.7)	27.7 (4.0)
	Week 3	15.6 (3.7)	13.1 (4.5)	25.4 (5.3)	27.0 (4.0)
	follow up	14.9 (4.1)	12.3 (5.1)	25.9 (5.8)	27.4 (4.1)
CGI	**baseline**	4.8 (0.6)	4.5 (0.6)	4.8 (0.7)	5.0 (0.7)
	Week 1	4.2 (0.6)	3.9 (0.5)	4.5 (0.8)	4.5 (0.7)
	Week 2	3.5 (0.5)	3.0 (0.7)	4.4 (0.8)	4.5 (0.7)
	Week 3	2.6 (0.7)	2.1 (0.9)	4.2 (0.8)	4.4 (0.7)
	follow up	2.5 (0.7)	1.9 (0.8)	4.3 (0.9)	4.5 (0.7)

A1: Active & 1 session/day, A2: Active & 2 sessions/day, S1: Sham & 1 session/day, S2: Sham & 2 sessions/day.

Table 4: Effect of HF rTMS given one or two sessions daily on symptoms of major depression: Mixed effects regression (random intercept and random slope) coefficients, referring to week s 1 to 3, adjusted for the baseline measures.

	HDRS				**CGI-S**			
	b	s.e.	z	p-value	b	s.e.	z	p-value
baseline	0.9	0.1	13.0	<0.001	0.6	0.1	8.2	<0.001
group[1]:								
A2	-1.8	1.0	-1.8	0.077	-0.3	0.2	-1.6	0.112
S1	11.0	1.1	10.3	<0.001	1.6	0.2	7.7	<0.001
S2	12.0	1.0	11.5	<0.001	1.7	0.2	8.4	<0.001
week[2]:								
1	10.2	0.5	22.2	<0.001	1.6	0.1	12.0	<0.001
2	4.5	0.4	12.3	<0.001	0.9	0.1	9.0	<0.001
group x week								
A2-1	1.4	0.6	2.1	0.036	0.2	0.2	1.1	0.257
A2-2	0.5	0.5	1.0	0.333	0.0	0.1	0.3	0.760
S1-1	-7.9	0.7	-11.4	<0.001	-1.3	0.2	-6.2	<0.001
S1-2	-3.3	0.6	-6.0	<0.001	-0.7	0.2	-4.6	<0.001
S2-1	-9.2	0.7	-13.6	<0.001	-1.5	0.2	-7.7	<0.001
S2-2	-3.9	0.5	-7.3	<0.001	-0.8	0.1	-5.5	<0.001
constant	-11.4	2.2	-5.1	<0.001	-0.4	0.4	-1.0	0.320

[1]reference category: A1. [2]reference category: week 3.
A1: Active & 1 session/day, A2: Active & 2 sessions/day,
S1: Sham & 1 session/day, S2: Sham & 2 sessions/day.